



FORM PTO-1390 U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE (MODIFIED)		ATTORNEY'S DOCKET NUMBER <b>X-11121</b>	
<b>TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371</b>		U.S. APPLICATION NO. (if known, see 37 C.F.R. 1.5) <b>10/048242</b>	
INTERNATIONAL APPLICATION NO. <b>PCT/US00/19549</b>	INTERNATIONAL FILING DATE <b>26 July 2000 (26.07.00)</b>	PRIORITY DATE CLAIMED <b>12 August 1999 (12.08.99)</b>	
TITLE OF INVENTION: <b>TOPICAL ORGANIC ECTOPARASITICIDAL FORMULATIONS</b>			
APPLICANT(S) FOR DO/EO/US: <b>James Web Kassebaum, Paul Thomas Pugh, and William Webster Thompson</b>			
Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:			
<ol style="list-style-type: none"> <li>1. <input checked="" type="checkbox"/> This is a <b>FIRST</b> submission of items concerning a filing under 35 U.S.C. 371.</li> <li>2. <input type="checkbox"/> This is a <b>SECOND</b> or <b>SUBSEQUENT</b> submission of items concerning a filing under 35 U.S.C. 371.</li> <li>3. <input type="checkbox"/> This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).</li> <li>4. <input checked="" type="checkbox"/> A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.</li> <li>5. <input checked="" type="checkbox"/> A copy of the International Application as filed (35 U.S.C. 371(c)(2))           <ol style="list-style-type: none"> <li>a. <input type="checkbox"/> is transmitted herewith (required only if not transmitted by the International Bureau).</li> <li>b. <input type="checkbox"/> has been transmitted by the International Bureau.</li> <li>c. <input checked="" type="checkbox"/> is not required, as the application was filed in the United States Receiving Office (RO/US).</li> </ol> </li> <li>6. <input type="checkbox"/> A translation of the International Application into English (35 U.S.C. 371(c)(2)).</li> <li>7. <input checked="" type="checkbox"/> Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))           <ol style="list-style-type: none"> <li>a. <input type="checkbox"/> are transmitted herewith (required only if not transmitted by the International Bureau).</li> <li>b. <input type="checkbox"/> have been transmitted by the International Bureau.</li> <li>c. <input type="checkbox"/> have not been made; however, the time limit for making such amendments has NOT expired.</li> <li>d. <input checked="" type="checkbox"/> have not been made and will not be made.</li> </ol> </li> <li>8. <input type="checkbox"/> A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).</li> <li>9. <input type="checkbox"/> An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).</li> <li>10. <input checked="" type="checkbox"/> A copy of the International Preliminary Examination Report (IPER), including any annexes, and, if not in English, an English language translation of the annexes to the IPER under PCT Article 36 (35 U.S.C. 371(c)(5)).</li> </ol>			
<b>Items 11. to 16. below concern document(s) or information included:</b>			
<ol style="list-style-type: none"> <li>11. <input type="checkbox"/> An Information Disclosure Statement under 37 CFR 1.97 and 1.98.</li> <li>12. <input checked="" type="checkbox"/> An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.</li> <li>13. <input checked="" type="checkbox"/> A <b>FIRST</b> preliminary amendment.  <input type="checkbox"/> A <b>SECOND</b> or <b>SUBSEQUENT</b> preliminary amendment.</li> <li>14. <input type="checkbox"/> A substitute specification.</li> <li>15. <input type="checkbox"/> A change of power of attorney and/or address letter.</li> <li>16. <input type="checkbox"/> Other items or information:</li> </ol>			

JC03 Rec'd PCT/PTO 24 JAN 2002

U.S. APPLICATION NO. (if known, see 37 C.F.R. 1.5) <b>10/048242</b>		INTERNATIONAL APPLICATION NO. <b>PCT/US00/19549</b>		ATTORNEY'S DOCKET NUMBER <b>X-11121</b>	
17. <input checked="" type="checkbox"/> The following fees are submitted:  <b>BASIC NATIONAL FEE (37 CFR 1.492(a)(1)-(5)):</b> Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO. <b>\$1040.00</b>  International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO ..... <b>\$890.00</b>  International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO..... <b>\$750.00</b>  International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4) ..... <b>\$710.00</b>  International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4) ..... <b>\$100.00</b>  <b>ENTER APPROPRIATE BASIC FEE AMOUNT =</b>				<b>CALCULATIONS PTO USE ONLY</b>	
				<b>\$ 890.00</b>	
Surcharge of <b>\$130.00</b> for furnishing the oath or declaration later than <u>  20  </u> <u>  30  </u> months from the earliest claimed priority date (37 CFR 1.492(e)).				<b>\$</b>	
CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	35 -20=	15	X \$18.00	<b>\$ 270.00</b>	
Independent claims	3 -3=	0	X \$84.00	<b>\$</b>	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ \$280.00	<b>\$ 280.00</b>	
<b>TOTAL OF ABOVE CALCULATIONS =</b>				<b>\$ 550.00</b>	
Reduction by 1/2 for filing by small entity, if applicable. Verified Small Entity Statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28).				<b>\$</b>	
<b>SUBTOTAL =</b>				<b>\$ 1,440.00</b>	
Processing fee of <b>\$130.00</b> for furnishing English translation later than <u>  20  </u> <u>  30  </u> months from the earliest claimed priority date (37 CFR 1.492(f)).				<b>\$</b>	
<b>TOTAL NATIONAL FEE =</b>				<b>\$ 1,440.00</b>	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). <b>\$40.00 per property</b>				<b>\$</b>	
<b>TOTAL FEES ENCLOSED =</b>				<b>\$ 1,440.00</b>	
				Amount to be refunded	<b>\$</b>
				charged	<b>\$</b>
a. <input type="checkbox"/> A check in the amount of \$_____ to cover the above fees is enclosed. b. <input checked="" type="checkbox"/> Please charge my Deposit Account No. 05-0840 in the amount of <b>\$1,440.00</b> to cover the above fees. A duplicate copy of this sheet is enclosed. c. <input checked="" type="checkbox"/> The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 05-0840. A duplicate copy of this sheet is enclosed.					
<b>NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.</b>					
<b>SEND ALL CORRESPONDENCE TO:</b> <b>ELI LILLY AND COMPANY</b> PATENT DIVISION/JCD LILLY CORPORATE CENTER INDIANAPOLIS, IN 46285  <u>Jan 24, 2002</u> DATE  <u>30,167</u> REGISTRATION NUMBER		 SIGNATURE  <u>John C. Demeter</u> NAME  <u>(317) 276-3785</u> TELEPHONE NUMBER		 <b>25885</b> PATENT TRADEMARK OFFICE	

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"Express Mail" mailing label number EL 230530170 US

Date of Deposit

Jan. 24, 2002

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 C.F.R. 1.10 on the date indicated above and is addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

GULZEN OTTOMAS

Printed Name

Dylen Thomas

Signature

**PATENT APPLICATION****IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Applicants : James Web Kassebaum, et al. )  
)  
For : TOPICAL ORGANIC )  
ECTOPARASITICIDAL FORMULATIONS) )  
)  
Docket No. : X-11121 )

**PRELIMINARY AMENDMENT**

Assistant Commissioner for Patents

Washington, D. C. 20231

Sir:

**In the Claims**

Please add the following new Claims 12, 13, 14 and 15.

12. (new) A topical ectoparasiticide formulation comprising from 0.1 to 25 weight percent of a spinosyn, or a physiologically acceptable derivative or salt thereof; from 25 to 99 weight percent of isopropyl myristate and from 0.6 to 40 weight percent of a miscibilizing agent compatible with organic solvent systems, selected from acetic, lauric, octanoic, oleic and benzoic acids and N-methyl-2-pyrrolidinone.

13. (new) A formulation of Claim 1 wherein the miscibilizing agent is oleic acid.

14. (new) An article of manufacture, comprising packaging material and contained within said packaging material a topical formulation for controlling an ectoparasite infestation on a small ruminant or companion animal, wherein said formulation comprises

a topical unit dose of a formulation of Claim 1 or 2; and, wherein said packaging material comprises a label or package insert with instructions for topically administering

the dose to the animal.

15. (new) A method of controlling an ectoparasite infestation on a small ruminant or companion animal, comprising topically applying to the animal a formulation of Claim 1 or 2.

Remarks

Claims 1-15 are pending in this application. No claims have been allowed.

Enclosed as Attachment 1 is a clean form of new Claims 12, 13, 14 and 15, in accordance with 37 C.F.R. 1.121(c)(1)(i). Also, enclosed as Attachment 2 is a clean version of all pending claims, in accordance with 37 C.F.R. 1.121(c)(3).

New Claims 12, 13, 14 and 15 have been added to reflect features of the present invention that are more closely aligned with the disclosure and examples in the present case. These new claims are substantially based at least upon originally filed Claims 1, 2, 3 and 4 and Examples 3(c) and 4-10; page 7, lines 4-8 of the disclosure; Claim 7; and Claim 8, respectively.

Applicants respectfully contend no new matter is added by Claims 12, 13, 14 and 15.

Applicants respectfully request favorable consideration of this application in view of the claims submitted.

Respectfully submitted,



John C. Demeter  
Attorney for Applicants  
Registration No. 30,167  
Phone: 317-276-3785

Eli Lilly and Company  
Patent Division/JCD  
Lilly Corporate Center  
Indianapolis, Indiana 46285

January 10, 2002

ATTACHMENT 1  
(New Claims)

12. (new) A topical ectoparasiticide formulation comprising from 0.1 to 25 weight percent of a spinosyn, or a physiologically acceptable derivative or salt thereof; from 25 to 99 weight percent of isopropyl myristate and from 0.6 to 40 weight percent of a miscibilizing agent compatible with organic solvent systems, selected from acetic, lauric, octanoic, oleic and benzoic acids and N-methyl-2-pyrrolidinone.

13. (new) A formulation of Claim 1 wherein the miscibilizing agent is oleic acid.

14. (new) An article of manufacture, comprising packaging material and contained within said packaging material a topical formulation for controlling an ectoparasite infestation on a small ruminant or companion animal, wherein said formulation comprises

a topical unit dose of a formulation of Claim 1 or 2; and, wherein said packaging material comprises a label or package insert with instructions for topically administering the dose to the animal.

15. (new) A method of controlling an ectoparasite infestation on a small ruminant or companion animal, comprising topically applying to the animal a formulation of Claim 1 or 2.

ATTACHMENT 2  
(Pending Claims)

1. A topical ectoparasiticide formulation comprising: from about 0.1 to about 25 weight percent of an ectoparasiticide, selected from a spinosyn, or a physiologically acceptable derivative or salt thereof, and cyperpyrethrin; from about 25 to about 99.9 weight percent of a (C<sub>3</sub>-C<sub>6</sub>) branched alkyl (C<sub>10</sub>-C<sub>20</sub>) alkanooate spreading agent; and up to about 70 weight percent of a miscibilizing agent compatible with organic solvent systems.

2. A formulation of Claim 1 wherein the spreading agent is a (C<sub>3</sub>-C<sub>6</sub>) branched alkyl (C<sub>12</sub>-C<sub>16</sub>) alkanooate.

3. A formulation of Claim 2 wherein the (C<sub>3</sub>-C<sub>6</sub>) branched alkyl (C<sub>12</sub>-C<sub>16</sub>) alkanooate is isopropyl myristate.

4. A formulation of Claim 1, 2 or 3 wherein the miscibilizing agent is selected from formic, acetic, propionic, benzoic, butyric, valeric, caproic, enanthic, caprylic, pelargonic, capric, undecylic, lauric, tridecylic, myristic, pentadecylic, palmitic, margaric, stearic, oleic, arachidic, behenic, lignoceric, cerotic, montanic, triacontanoic, psyllic, or ceroplastic acids.

5. A formulation of Claim 1, 2 or 3 or 4, which further comprises a miscibilizing agent selected from benzyl alcohol, ethylene glycol phenyl ether, D-limonene, N-methyl-2-pyrrolidinone, methylated soybean oils and soybean oil methyl esters.

6. A formulation of Claim 1, 2, 3, 4 or 5 which further comprises an effective amount of an antimicrobial agent.

7. An article of manufacture, comprising packaging material and contained within said packaging material a topical formulation for controlling an ectoparasite infestation on a small ruminant or companion animal, wherein said formulation comprises

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a topical unit dose of a formulation of Claim 1, 2, 3, 4, 5 or 6; and,  
wherein said packaging material comprises a label or package insert with instructions for topically administering the dose to the animal.

8. A method of controlling an ectoparasite infestation on a small ruminant or companion animal, comprising topically applying to the hair and/or skin of the animal a formulation of Claim 1, 2, 3, 4, 5 or 6.

9. The method of Claim 8 wherein the formulation is applied using a spot-on protocol.

10. The method of Claim 8 wherein the formulation is applied using a pour-on protocol.

11. A topical ectoparasiticide formulation comprising from about 0.1 to about 25 weight percent of an ectoparasiticide, selected from spinosyn or a physiologically acceptable derivative or salt thereof, and cyperpyrethrin, from about 25 to about 99.9 weight percent of a (C3-C6) branched alkyl (C10-C20) alkanoate spreading agent, and up to about 70 weight percent of a miscibilizing agent compatible with organic solvent systems, substantially as hereinbefore described with reference to any one of the Examples.

12. A topical ectoparasiticide formulation comprising from 0.1 to 25 weight percent of a spinosyn, or a physiologically acceptable derivative or salt thereof; from 25 to 99 weight percent of isopropyl myristate and from 0.6 to 40 weight percent of a miscibilizing agent compatible with organic solvent systems, selected from acetic, lauric, octanoic, oleic and benzoic acids and N-methyl-2-pyrrolidinone.

13. A formulation of Claim 1 wherein the miscibilizing agent is oleic acid.

14. An article of manufacture, comprising packaging material and contained within said packaging material a topical formulation for controlling an ectoparasite

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infestation on a small ruminant or companion animal, wherein said formulation comprises

a topical unit dose of a formulation of Claim 1 or 2; and, wherein said packaging material comprises a label or package insert with instructions for topically administering the dose to the animal.

15. A method of controlling an ectoparasite infestation on a small ruminant or companion animal, comprising topically applying to the animal a formulation of Claim 1 or 2.



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## TOPICAL ORGANIC ECTOPARASITICIDAL FORMULATIONS

This invention relates to topical organic ectoparasiticide formulations. Ectoparasites such as fleas, blowflies, lice, ticks and mites can seriously affect productivity in the domesticated animal industries. Further, such parasites cause disease and discomfort for pets and other companion animals. Ectoparasites are often controlled by topically applying an insecticide or mixture of insecticides onto the animal. Topical ectoparasite control agents are usually applied in liquid formulations. The formulations can be applied by spot-on application, plunge or spray dipping, jetting with a hand held spray or in a race, or as a back-line spray or pour-on.

A particular problem with topical formulations is poor migration from the site of application. In the sheep industry, for example, treatment for ectoparasites is commonly carried out in the early season within 24 hours after shearing, or, less frequently, later in the season when the wool is longer. Especially with early season treatments, when the topical formulation is applied along the dorsal midline or back-line of the animal, the insecticide component of currently available commercial formulations migrates very poorly from the application site. Typically less than 10% of the applied insecticide diffuses away from the application site within the first 10 days. Thus, extensive areas of the animal's skin and/or hair may receive sublethal concentrations of the insecticide. These areas remain susceptible to damaging invasion by ectoparasites.

To overcome the inadequate control caused by poor migration of the insecticide, it has become common in the industry to apply relatively large amounts of insecticide. This practice introduces unwelcome costs, results in the presence of insecticide residues in certain animal products (such as wool and wool byproducts) and increases the potential of environmental pollution. It also increases the risk of unwanted and unnecessary exposure to pesticides to animal handlers and farmers treating the animals.

Solvent-based formulations have received attention in recent times in the search for greater insecticide mobility that would allow the same insecticidal effect to be achieved with less insecticide in the formulations. Up to the present, there

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has been little success in identifying a solvent that materially enhances the spread of insecticides that are applied using a spot-on or pour-on method.

This invention provides insecticidal formulations that can be applied topically to animals and that have the advantage of permitting the active ingredient to spread over the surface of the skin and/or hair of the treated animal, thereby providing more extensive coverage of the insecticide. These formulations, therefore, provide greater inhibition or eradication of ectoparasites with smaller amounts of insecticide.

The topical ectoparasiticide formulations of this invention comprise an ectoparasiticide, a spreading agent and optionally a miscibilizing agent. More specifically, the invention relates to a topical ectoparasiticide formulation comprising from about 0.1 to about 25 weight percent of an ectoparasiticide, from about 25 to about 99.9 weight percent of a (C<sub>3</sub>-C<sub>6</sub>) branched alkyl (C<sub>10</sub>-C<sub>20</sub>) alkanoate spreading agent, and optionally up to about 70 weight percent of a miscibilizing agent compatible with organic solvent systems.

An exemplary topical ectoparasiticide formulation of this invention is one wherein the ectoparasiticide is a spinosyn, or a physiologically acceptable derivative or salt thereof.

This invention also encompasses a method of controlling an ectoparasite infestation on a small ruminant or companion animal, comprising topically applying to the hair and/or skin of the animal a formulation comprising from about 0.1 to about 25 weight percent of a spinosyn, or a physiologically acceptable derivative or salt thereof, from about 25 to 99.9 weight percent isopropyl myristate, and from 0 to about 70 weight percent of a miscibilizing agent compatible with organic solvent systems.

The invention also relates to an article of manufacture, comprising packaging material and a topical formulation for controlling an ectoparasite infestation on a small ruminant or companion animal contained within said packaging material, wherein said formulation comprises

a topical unit dose of a formulation comprising 0.1 to about 25 weight percent of an ectoparasiticide, from about 25 to about 99.9 weight percent of a (C<sub>3</sub>-C<sub>6</sub>) branched alkyl (C<sub>10</sub>-C<sub>20</sub>) alkanoate spreading

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agent, and optionally up to about 70 weight percent of a miscibilizing agent compatible with organic solvent systems; and, wherein said packaging material comprises a label or package insert with instructions for topically administering the dose to the animal.

5           This article of manufacture or kit is particularly appropriate when the companion animal is a dog or a cat. The timing of administering the doses will generally be every 30 days. Each kit typically contains a sufficient number of doses to control the ectoparasite infestation for a period of several months.

          This invention further provides a topical formulation for controlling an  
10   ectoparasite infestation on a small ruminant or companion animal comprising a spinosyn, or a derivative or salt thereof, and a spreading agent substantially as hereinbefore described with references to any one of the Examples.

          Examples of small ruminant animals are a sheep, a goat or a camellid.

          The term "companion animal" includes dogs, cats, horses and other  
15   pets owned and maintained in close association with humans as part of the human-animal bond.

          The term "controlling" as used herein refers to either ameliorating or eliminating a current infestation or preventing an infestation in a susceptible host.

          Many insecticidal agents are useful in the formulations of this  
20   invention. Indeed, any ectoparasiticide compound that is soluble in a (C<sub>3</sub>-C<sub>6</sub>) branched alkyl (C<sub>10</sub>-C<sub>20</sub>) alkanoate vehicle and is useful for topical application can be incorporated as the insecticidal component of these formulations. Typically, the insecticidal agent is active against a broad spectrum of pest species, including acaricides, antiparasitic agents, insect growth regulators and compounds that inhibit or  
25   kill flies, flying pests and other "temporary" pests that only alight momentarily on domesticated animals.

          Examples of useful classes of insecticides are spinosyns, organophosphates, organochlorines, carbamates, and pyrethrins. Specific useful insecticidal compounds include tetraethyl pyrophosphate (TEPP), mevinphos,  
30   disulfoton, azinphosmethyl, parathion, methylparathion, chlorfenvinphos, cichlorvos, diazinon, dimethoate, trichlorfon, chlorothion, malathion, ronnel, abate, baygon, carbaryl, mobam, temik, zectran, methoxychlor, aldrin, dieldrin, endrin, heptachlor,

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chlordane, lindane, mirex, nicotine, rotenoids, pyrethrums, spinosyns and synthetic pyrethroids, including cypermethrin.

Preferred insecticides useful in these formulations are spinosyns or a pyrethroid such as cypermethrin.. Spinosyns are especially preferred.

5           The spinosyns (also known as A83453 factors) are agricultural insecticides that have shown activity against southern armyworm and other insects in the order *Lepidoptera*, and cotton aphid and other members of the order *Homoptera*. (See, for example, U.S. Patent No. 5,571,901).

10           The spinosyns were also known to have some ectoparasiticial activity, i.e., they had *in vitro* activity against mosquito larvae, black blowfly larvae and adult stable flies, which are members of the insect order *Diptera*, and transient systemic activity against larval blowfly and adult stable fly in guinea pigs and sheep. For these tests, the spinosyns were administered in aqueous polyvinylpyrrolidone or in polyethylene glycol (see U.S. Patent No. 5,571,901, col. 26-32).

15           The spinosyns are naturally-derived macrolides produced by fermentation of *Saccharopolyspora spinosa*. The fermentation produces multiple factors, including spinosyn A and spinosyn D (also called A83543A and A8354D). Spinosyn A and spinosyn D are the two spinosyns that are most active as insecticides. An agricultural product comprised mainly of these two spinosyns is available  
20           commercially under the name "spinosad".

          Spinosyn A was the first spinosyn isolated and identified from the fermentation broth of *Saccharopolyspora spinosa*. Subsequent examination of the fermentation broth revealed that *S. spinosa* produced a number of spinosyns that have been called spinosyns A to H and J. Additional spinosyns, denominated K to W,  
25           have been identified from various strains of *S. spinosa*. The various spinosyns are characterized by differences in the substitution patterns on the amino group of the forosamine, at selected sites on the tetracyclic ring system and on the 2N,3N,4N-(tri-O-methyl)rhamnose group.

          Boeck et al. described spinosyns A-H and J (which they called A83543  
30           factors A, B, C, D, E, F, G, H and J), and salts thereof, in U.S. Patent Nos. 5,362,634 (issued Nov. 8, 1994); 5,496,932 (issued March 5, 1996); and 5,571,901 (issued Nov. 5, 1996). Mynderse et al. described spinosyns L-N (which they called A83543

factors L, M and N), their N-dimethyl derivatives, and salts thereof, in U.S. Patent No. 5,202,242 (issued Apr. 13, 1993); and Turner et al. described spinosyns Q-T (which they called A83543 factors Q, R, S and T), their N-dimethyl derivatives, and salts thereof, in U.S. Patent Nos. 5,591,606 (issued January 7, 1997) and 5,631,155 (issued May 29, 1997). Spinosyns K, O, P, U, V, W and Y are described, for example, by Carl V. DeAmicis, James E. Dripps, Chris J. Hatton and Laura I. Karr in American Chemical Society's Symposium Series: Phytochemicals for Pest Control, Chapter 11, "Physical and Biological Properties of Spinosyns: Novel Macrolide Pest-Control Agents from Fermentation", pages 146-154 (1997).

10 The spinosyns can be isolated in the form of salts that are also useful in the formulations of this invention. The salts are prepared using standard procedures for salt preparation. For example, spinosyn A can be neutralized with an appropriate acid to form an acid addition salt. Representative suitable acid addition salts include salts formed by reaction with either an organic or inorganic acid, for example, 15 sulfuric, hydrochloric, phosphoric, acetic, succinic, citric, lactic, maleic, fumaric, cholic, pamoic, mucic, glutamic, camphoric, glutaric, glycolic, phthalic, tartaric, formic, lauric, stearic, salicylic, methanesulfonic, benzenesulfonic, sorbic, picric, benzoic, cinnamic and like acids.

The term a "spinosyn or a derivative thereof" as used herein refers to an individual spinosyn factor (spinosyn A, B, C, D, E, F, G, H, J, K, L, M, N, O, P, Q, R, S, T, U, V, W or Y), an N-dimethyl derivative of one or more spinosyn factor, or a combination thereof. For convenience, the term "spinosyn component" as used means an individual spinosyn or a physiologically acceptable derivative or salt thereof, or a combination thereof. "Spinosad" as used herein refers to a mixture of spinosyns 25 comprised mainly of spinosyns A and D.

The spinosyns are known to have excellent human and animal safety and toxicological profiles. Because of their low toxicity to animals and humans, spinosyns are considered to be environment-friendly, "green" insecticides. It is desirable to formulate spinosyns to maintain this "green" profile.

30 Spinosyns have recently been found to be useful in the eradication or control of ectoparasites on sheep and companion animals. Thus, formulations of

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spinosyns with low toxicity and increased stability are potentially valuable in combating ectoparasites and the diseases such pests often carry.

The present formulations further comprise a (C<sub>3</sub>-C<sub>6</sub>) branched alkyl (C<sub>10</sub>-C<sub>20</sub>) alkanoate. This component is an organic solvent that acts as a spreading agent. Spreading agents increase the spreading of, and aid in substantially equalizing the distribution of, the active ingredient over the hair and/or skin surface area of the animal over time. The spreading agent solvent system should be safe, non-toxic, environment-friendly and non-flammable.

The branched alkyl portion of the (C<sub>3</sub>-C<sub>6</sub>) branched alkyl (C<sub>10</sub>-C<sub>20</sub>) alkanoate includes all branched chain isomers of C<sub>3</sub>-C<sub>6</sub> alkyl groups. Examples are isopropyl, isobutyl, isopentyl, and isohexyl. The (C<sub>10</sub>-C<sub>20</sub>) alkanoate moiety includes all C<sub>10</sub>-C<sub>20</sub> fatty alkanoate groups, including but not limited to, decanoate (C<sub>10</sub>), hendecanoate (C<sub>11</sub>), dodecanoate (C<sub>12</sub>), tridecanoate (C<sub>13</sub>), tetradecanoate (C<sub>14</sub>), pentadecanoate (C<sub>15</sub>), hexadecanoate (C<sub>16</sub>), heptadecanoate (C<sub>17</sub>), octadecanoate (C<sub>18</sub>), and eicosanoate (C<sub>20</sub>). Preferably, the spreading agent is a (C<sub>3</sub>-C<sub>6</sub>) branched alkyl (C<sub>12</sub>-C<sub>16</sub>) alkanoate. Of these solvents, C<sub>3</sub>- branched alkyl-C<sub>14</sub> alkanoates are especially useful. A preferred spreading agent is isopropyl myristate (IPM).

The formulations can optionally contain a miscibilizing agent. The miscibilizing agent aids in solubilizing the active ingredient and must be compatible with organic solvent systems. The phrase "compatible with organic solvent systems" means that the miscibilizing agent does not form more than one phase when mixed with the (C<sub>3</sub>-C<sub>6</sub>) branched alkyl (C<sub>10</sub>-C<sub>20</sub>) alkanoate component.

Suitable miscibilizing agents for use in these formulations generally are (C<sub>1</sub>-C<sub>30</sub>) organic acids. Typically, such organic acids are straight-chain saturated fatty acids, but they can also be low molecular weight organic acids such as formic acid, acetic acid, propionic acid and benzoic acid.

The choice of miscibilizing agent will vary depending on the insecticide in the formulation. When the insecticide component is a spinosyn, examples of suitable miscibilizing agents are formic acid, acetic acid, propionic acid, butyric acid, valeric acid, caproic acid, benzoic acid, enanthic acid, caprylic acid, pelargonic acid, capric acid, undecylic acid, lauric acid, tridecylic acid, myristic acid, pentadecylic acid, palmitic acid, margaric acid, stearic acid, oleic, arachidic acid, behenic acid,

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lignoceric acid, cerotic acid, montanic acid, triacontanoic acid, psyllic acid, and ceroplastic acid. Other useful miscibilizing agents are (C<sub>1</sub>-C<sub>30</sub>) alkyl sulfuric acids, (C<sub>1</sub>-C<sub>30</sub>) alkyl phosphoric acids, and (C<sub>1</sub>-C<sub>30</sub>) alkyl sulfonic acids.

In formulations containing a spinosyn solubilized in isopropyl myristate, for example, oleic acid is a particularly useful miscibilizing agent because it aids in solubilizing the spinosyn (thus allowing for the formation of solvent solutions containing relatively high concentrations of active ingredient), and it is compatible with the isopropyl myristate component.

Compounds other than (C<sub>1</sub>-C<sub>30</sub>) organic acids can also be useful miscibilizing agents in the formulations of this invention. In general, a miscibilizing compound useful for these formulations: 1) is compatible with the selected organic solvent component, and 2) solubilizes the active ingredient without substantially altering the spreading properties of the formulation.

When insecticide is a spinosyn and the spinosyn component is spinosyn D or spinosad (i.e., a mixture of spinosyns A and D), it is especially important that the miscibilizing agent is able to solubilize the spinosyn D sufficiently. In technical grade spinosad, factor D is generally the factor that causes solubility problems when preparing spinosad-containing formulations. Examples of miscibilizing agents that are useful for spinosad-containing ectoparasiticial formulations of the present invention include, but are not limited to, benzyl alcohol, ethylene glycol phenyl ether, D-limonene, N-methyl-2-pyrrolidinone, and methylated soybean oils and soybean oil methyl esters, such as SOYGOLD 1000 (AG Environmental Products LLC).

The present formulations can also contain other optional ingredients, such as: antioxidants, UV-absorbing compounds or photostabilizers, viscosity-modifying agents, antimicrobial agents, dyes, perfumes, deodorants and physiologically or dermatologically acceptable carriers, diluents, excipients or adjuvants. Such agents are known in the art.

For example, one or more antioxidants can be added to the formulations in an amount effective to retard oxidation of the formulation components and the ensuing degradative effects. Potentially useful antioxidants include primary

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antioxidants that are radical scavengers, such as hindered phenolics and secondary amines, and secondary antioxidants, such as phosphites and thioesters that function as peroxide decomposers. Preferred antioxidants for use in these formulations are blends of primary and secondary antioxidants, including particularly blends of phenolic and phosphite antioxidant compositions.

There are many commercially available antioxidants products designed for polymer stabilization, including antioxidant formulations comprising synergistic combinations of primary and secondary antioxidants. Examples of commercially available antioxidants useful in the formulations of this invention include the

10. Irganox® antioxidants available from Ciba Geigy, Vanox® antioxidants from R.T. Vanderbilt, and the Naugard® antioxidants available from Uniroyal Chemicals.

When the formulations include an antimicrobial component, it should be present in an amount effective to prevent the growth of microorganisms in the formulation.

15                    Generally, the formulations of this invention can be prepared by  
blending the components with adequate mixing or stirring. For example, a useful  
spinosad formulation is one having a final concentration of 2 mg of spinosad per mL.  
One such formulation is prepared to contain 99.1 weight percent IPM, 0.6 weight  
percent oleic acid, and 0.3 weight percent spinosad technical (89% active ingredient).  
20       This formulation is made by adding the appropriate amount of spinosad to the IPM  
solvent with mixing or stirring, blending the oleic acid into the IPM/spinosad mixture,  
and continuing the mixing or stirring until the spinosad has completely solubilized to  
form the final formulation product. An optional additional step is to filter the final  
formulation to remove any impurities or extraneous materials.

The formulations of this invention are applied to the animal topically. Topical control protocols include spot-on or pour-on treatments wherein the formulation is placed directly onto a discreet skin and/or hair surface area of the animal and allowed to spread over the remainder of the animal's skin or hair surface area. Generally, spot-on or pour-on protocols involve initially placing the formulation on the dorsal midline (i.e., the head, neck, shoulders or back) of the animal. Placement typically occurs on a dorsal midline surface area that constitutes less than 10% of the animal's entire surface area. For example, a typical pour-on treatment



protocol involves applying about 4 to about 50 mL of a liquid ectoparasiticial formulation in a narrow strip along the backline of an animal, from the withers to the tail or rump.

- For spot-on or pour-on treatment to control ectoparasites, such as lice,
- 5 which are present over the whole surface of an animal, the ectoparasiticial active ingredient must spread from the narrow strip at the backline to cover the entire surface of the animal. The present formulations have this advantageous spreading effect. Of course, they can be applied to areas of skin that constitute greater than 10% of the surface area of the animal, but such applications limit the advantage offered by these
- 10 formulations. Another advantage of these formulations is that they offer extended ectoparasiticial coverage and need not be applied more than weekly or biweekly at most.

#### Example 1

15 Wetting Tests for Various Solvent Systems

- To determine organic solvents that are useful spreading agents, solvent systems that are capable of solubilizing at least 1% spinosad by weight percent were screened for hair wetting by applying about 1 mL of the solvent system (solvents were screened without active ingredient), dropwise, to a tanned rabbit pelt that was at an
- 20 angle of about 45°. Solvent systems that wet the rabbit hair and did not run off before wetting the hair were considered to pass the screen. Table I describes the ability of selected organic solvents to wet the rabbit hair.

**Table I. Ability of Solvents and Aqueous Surfactant Systems to Wet Rabbit Hair on Tanned Rabbit Pelts.**

<b><u>Organic Solvent</u></b>	
<b><u>Wet Well</u></b>	<b><u>Did Not Wet</u></b>
isopropyl myristate	triacetin
methyl laurate	N-methyl pyrrolidone
dipropylene glycol methyl ether	propylene glycol
butyl lactate	
methyl caprate	
methyl oleate	
octanoic acid	
limonene	
hexanol	
ethyl oleate	

As Table I shows, water immiscible, nonpolar solvents generally wet well, although dipropylene glycol methyl ether is water miscible and did wet the hair very well.

#### **Example 2**

##### **Formulation Spreading Tests**

Further studies were conducted to determine the abilities of various solvents to aid in spreading of active ingredient.

International Patent Application WO 9524219 teaches that wool grease fraction (F1) provides superior spreading of pyrethroid insecticides on sheep when compared to organic solvent spreading agents. Tests were conducted to compare the spreading properties of formulations containing the F1 wool grease fraction and various organic solvents. The amount and rate of diffusion of <sup>14</sup>C-labeled zeta-cypermethrin from the dorsal midline of sheep were determined when applied in F1 wool grease fraction and a range of test excipients. Four formulations containing 10

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mg/mL zeta-cypermethrin spiked with 100  $\mu\text{Ci}$  [ $^{14}\text{C}$ ] zeta-cypermethrin were prepared in the following vehicles: wool grease fraction F1, isopropyl myristate, octyl stearate and glyceryl tricaprilate/caprato. A dose of 1 mL/5kg body weight of each formulation was applied to the backline of 3 sheep. Wool was collected and pooled 1, 2, 4, 8, 11 and 14 days after treatment from three 12 x 12 mm squares chosen at random, along meridian lines drawn 2, 7.5 and 15 cm down the side of each sheep from the backline. The clipped areas were also swabbed. At day 14 after treatment the wool at the site of application was collected, and back and perirenal fat samples were collected. The quantity of zeta-cypermethrin in each sample was measured by liquid scintillation counting.

For the majority of the measurements taken, isopropyl myristate gave the greatest spread of zeta-cypermethrin and the wool grease fraction F1 provided the least spreading. When the vehicle was the F1 wool grease fraction, only the 2-cm meridian showed increased concentration of zeta-cypermethrin over time after initial application. When the vehicle was isopropyl myristate, the quantity of zeta-cypermethrin measured at all meridians increased with time following administration. Octyl stearate and glyceryl tricaprilate/caprato gave modest spread, but not as great as the spread provided by the IPM formulations. Tissue residues were similar amongst formulations except the glyceryl tricaprilate/caprato formulation appeared to cause the highest residue levels.

After two weeks it was determined that F1 was a comparatively poor spreading agent, octyl stearate and glyceryl tricaprilate/caprato provided better spreading properties, and isopropyl myristate gave the best spread of zeta-cypermethrin.

### Example 3

#### Ectoparasitocidal Efficacy Tests of Wool Grease and IPM Formulations

Tests were conducted to compare the efficacy of formulations of spinosad in F1 wool grease fraction versus those in isopropyl myristate against lice on sheep. Two F1 formulations containing spinosad at 2 mg/mL and 10 mg/mL, and one formulation containing 2 mg/mL spinosad in isopropyl myristate were made as follows:

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a) F1 Formulation (2 mg/mL)

81.11 % F1

18.62 % solvent (50/50 petroleum ether/acetone)

0.27 % spinosad technical that was 89% active

100 % (w/w)

Formulation density = 0.84 g/mL

b) F1 Formulation (10 mg/mL)

80.26 % F1

18.42 % solvent (50/50 petroleum ether/acetone)

1.32 % spinosad technical that was 89% active

100 %

Formulation density = 0.84 g/mL

c) IPM Formulation (2 mg/mL)

99.123 % IPM

0.613 % oleic acid

0.264 % spinosad technical that was 89% active

100 %

Formulation density = 0.85 g/mL

Each formulation was administered to sheep as a pour-on application immediately after shearing. Spinosad/F1 formulations were tested at doses of 0 (i.e., vehicle alone), 0.4 and 2 mg/kg, while the spinosad/IPM formulation was tested at a dose of 0.4 mg/kg. The 2 mg/kg dose of spinosad/F1 was administered using the 10 mg/mL formulation, while the 0.4 mg/kg doses were administered using the 2 mg/mL formulations. Lice counts were taken on the sheep at sites all over the animal, including the head and neck. These lice counts were taken before treatment and on or about weekly for the following eight weeks. The results of this study are summarized in Table II.

**Table II: Comparison of Ectoparasiticial Efficacy of  
Spinosad in F1 and IPM Formulations in Sheep  
Lice Counts (mean)**

			Week of Study							
		<u>Day 0</u> <u>lice count</u>	<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>	<u>6</u>	<u>7</u>	<u>8</u>
5	F1 Only	643	428	328	350	237	245	159	156	145
	0.4 mg/kg Spinosad/F1	622	391	213	211	159	118	103	69	68
10	2 mg/kg Spinosad/F1	582	146	86	48	2	13	4	3	2
	0.4 mg/kg Spinosad/IPM	575	138	81	68	47	32	13	25	21

As the results summarized in Table II show, spinosad in IPM at a dose of 0.4 mg/kg was superior in lice control to spinosad in F1 at 0.4 mg/kg, and was almost equal in efficacy to spinosad in F1 at 2 mg/kg. Spinosad in IPM gave outstanding control of lice on sheep, including control of lice on the head and neck, which indicated that IPM potentiated the spreading of spinosad from the dorsal midline to the head, neck and other body surface regions.

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#### Example 4

#### Efficacy of Spinosad in Various Organic Solvents vs. Lice in Sheep

Further lice efficacy studies on sheep were conducted to compare the efficacy of IPM as a spreading agent to that of other organic solvent systems containing blends of organic solvents. The formulations tested had the following compositions:

- 25
- 30
- a) IPM Formulation:  
99.12 % IPM  
0.61 % oleic acid  
0.27 % spinosad technical (89% active)

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- 5      b)      OP/IPM Formulation  
79.78% octyl palmitate (OP)  
19.95% IPM  
0.27% spinosad technical (89% active)
- 10      c)      GTCC/OP Formulation  
79.78% glyceryl tricaprylate/caprate (GTCC)  
19.95% octyl palmitate  
0.27% spinosad technical (89% active)
- 15      d)      GTCC/IPM/CAP Formulation  
69.81% glyceryl tricaprylate/caprate  
14.96% IPM  
14.96% cetearyl octanoate (CAP)  
0.27% spinosad technical (89% active)
- 20      e)      OP/IPM/OSU Formulation  
69.81% octyl palmitate  
14.96% IPM  
14.96% dioctyl succinate (OSU)  
0.27% spinosad technical (89% active)
- 25      f)      TPM/LWG/GTCC Formulation  
59.84% tripropylene glycol methyl ether (TPM)  
19.95% liquid wool grease (LWG)  
19.95% glyceryl tricaprylate/caprate  
0.27% spinosad technical (89% active)
- 30      g)      TPM/OSU Formulation  
79.78% tripropylene glycol methyl ether  
19.95% dioctyl succinate  
0.27% spinosad technical (89% active)

35      Lice counts were taken on the sheep at sites all over the animal,  
including the head and neck. These lice counts were taken before treatment and on or  
about weekly for the following twelve weeks. The results of this study summarized in  
Table III.

**Table III: Efficacy of Spinosad in Organic Solvent Formulations vs. Lice in Sheep**  
**Lice Count (mean)**

	Treatment	Pretreatment lice count	Weeks					
			1	2	4	6	8	12
5	Control	253	197	128	163	206	162	204
	IPM	268	33	23	18	20	18	18
	OP/IPM	271	71	51	83	90	71	184
	GTCC/OP	257	32	28	40	52	46	106
	GTCC/IPM/CAP	278	28	16	24	25	22	33
10	OP/TPM/OSU	259	33	19	23	22	19	40
	TM/LWG/GTCC	267	53	29	39	34	27	48
	TPM/OSU	259	58	38	64	62	66	119

As Table III shows, spinosad in IPM alone was the most effective treatment of the 7 formulations tested. A strong correlation exists between the results of the spreading experiments and those of the field efficacy experiments. Spinosad formulations in IPM exhibited excellent spreading characteristics and demonstrated outstanding long-term protective and inhibitory effects against ectoparasiticide infestation in sheep.

Examples 5-11 illustrate various formulations of this invention.

**Example 5: Spinosad/IPM/acetic acid Formulation**

5.65% spinosad (88.5% active)  
 3% acetic acid  
 91.35% IPM

**Example 6: Spinosad/IPM/octanoic acid Formulation**

5.65% spinosad (88.5% active)  
 7.5% octanoic acid  
 86.85% IPM

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**Example 7: Spinosad/IPM/lauric acid Formulation**

5.65% spinosad (88.5% active)  
10.15% lauric acid  
84.2% IPM

5

**Example 8: Spinosad/IPM/oleic acid Formulation**

5.65% spinosad (88.5% active)  
16.5% oleic acid  
77.85% IPM

10

**Example 9: Spinosad/IPM/benzoic acid Formulation**

5.65% spinosad (88.5% active)  
3.76% benzoic acid  
90.59% IPM

15

**Example 10: Spinosad/IPM/NMP Formulation**

5.65% spinosad (88.5% active)  
40.0% 1-methyl-2-pyrrolidinone (NMP)  
54.35% IPM

20

**Example 11: Zeta-cypermethrin/IPM Formulation**

1.18% zeta-cypermethrin (84.7% active)  
98.82% IPM

25

The formulations of Examples 5-10 can be prepared by weighing the spinosad into a suitable container, adding the IPM and stirring to create a slurry, and then adding the final component and stirring until a clear solution is achieved. In preparing the formulation of Example 11, the zeta-cypermethrin is an oily liquid that requires gentle heating (approximately 40-50°C) to allow for proper mixing into the organic solvent phase. No separation of phases is evident upon cooling.

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ARTICLE 34

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CLAIMS

1. A topical ectoparasiticide formulation comprising: from about 0.1 to about 25 weight percent of an ectoparasiticide, selected from a spinosyn, or a physiologically acceptable derivative or salt thereof, and cyperpyrethrin; from about 25 to about 99.9 weight percent of a (C<sub>3</sub>-C<sub>6</sub>) branched alkyl (C<sub>10</sub>-C<sub>20</sub>) alkanooate spreading agent; and up to about 70 weight percent of a miscibilizing agent compatible with organic solvent systems.
2. A formulation of Claim 1 wherein the spreading agent is a (C<sub>3</sub>-C<sub>6</sub>) branched alkyl (C<sub>12</sub>-C<sub>16</sub>) alkanooate.
3. A formulation of Claim 2 wherein the (C<sub>3</sub>-C<sub>6</sub>) branched alkyl (C<sub>12</sub>-C<sub>16</sub>) alkanooate is isopropyl myristate.
4. A formulation of Claim 1, 2 or 3 wherein the miscibilizing agent is selected from formic, acetic, propionic, benzoic, butyric, valeric, caproic, enanthic, caprylic, pelargonic, capric, undecylic, lauric, tridecylic, myristic, pentadecylic, palmitic, margaric, stearic, oleic, arachidic, behenic, lignoceric, cerotic, montanic, triacontanoic, psyllic, or ceroplastic acids.
5. A formulation of Claim 1, 2, 3 or 4, which further comprises a miscibilizing agent selected from benzyl alcohol, ethylene glycol phenyl ether, D-limonene, N-methyl-2-pyrrolidinone, methylated soybean oils and soybean oil methyl esters.
6. A formulation of Claim 1, 2, 3, 4 or 5 which further comprises an effective amount of an antimicrobial agent.
7. An article of manufacture, comprising packaging material and contained within said packaging material a topical formulation for controlling an ectoparasite infestation on a small ruminant or companion animal, wherein said formulation comprises  
a topical unit dose of a formulation of Claim 1, 2, 3, 4, 5 or 6; and, wherein said packaging material comprises a label or package insert with instructions for topically administering the dose to the animal.
8. A method of controlling an ectoparasite infestation on a small ruminant or companion animal, comprising topically applying to the hair and/or skin

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of the animal a formulation of Claim 1, 2, 3, 4, 5 or 6.

9. The method of Claim 8 wherein the formulation is applied using a spot-on protocol.

10. The method of Claim 8 wherein the formulation is applied using a pour-on protocol.

11. A topical ectoparasiticide formulation comprising from about 0.1 to about 25 weight percent of an ectoparasiticide, selected from spinosyn or a physiologically acceptable derivative or salt thereof, and cyperpyrethrin, from about 25 to about 99.9 weight percent of a (C<sub>3</sub>-C<sub>6</sub>) branched alkyl (C<sub>10</sub>-C<sub>20</sub>) alkanolate spreading agent, and up to about 70 weight percent of a miscibilizing agent compatible with organic solvent systems, substantially as hereinbefore described with reference to any one of the Examples.

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- (71) Applicant (for all designated States except US): **ELI LILLY AND COMPANY** [US/US]; Lilly Corporate Center, Indianapolis, IN 46285 (US).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): **KASSEBAUM, James, Web** [US/US]; 9221 Leeward Court, Indianapolis, IN 46256 (US). **PUGH, Paul, Thomas** [US/US]; 8312 South Mill Road, Knightstown, IN 46148 (US). **THOMPSON, William, Webster** [US/US]; 5521 Overbrook Circle, Indianapolis, IN 46226 (US).
- (74) Agents: **DEMETER, John, C.** et al.; Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285 (US).
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(54) Title: TOPICAL ORGANIC ECTOPARASITICIDAL FORMULATIONS

(57) Abstract: This invention provides topical ectoparasiticide formulations comprising an ectoparasiticide, preferably a pyrethroid or a spinosyn, a spreading agent that is a (C<sub>3</sub>-C<sub>6</sub>) branched alkyl (C<sub>10</sub>-C<sub>20</sub>) alkanoate, preferably isopropyl myristate, and optionally a miscibilizing agent compatible with organic solvent systems, and methods of controlling an ectoparasite infestation on certain animals comprising topically applying such formulations to the animal.

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PTO/SB/01 (8-96) (MODIFIED)

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<b>DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION</b>	<b>Attorney Docket Number</b>	X-11121	
	<b>First Named Inventor</b>	James Web Kassebaum	
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	<b>Application Number</b>		
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<input type="checkbox"/> Declaration Submitted with Initial Filing	<b>Examiner Name</b>		
<input checked="" type="checkbox"/> Declaration Submitted after Initial Filing			

As a below named inventor, I hereby declare that:

My residence, post office address, and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

**TOPICAL ORGANIC ECTOPARASITICIDAL FORMULATIONS**

the specification of which  
☐ is attached hereto  
OR  
☒ was filed on 

26 July 2000

 as United States Application Number or PCT International (MM/DD/YYYY)

Application Number 

PCT/US00/19549

 and was amended on  (if applicable) (MM/DD/YYYY)

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37 Code of Federal Regulations, § 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code § 119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or § 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or of any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number(s)	Country	Foreign Filing Date (MM/DD/YYYY)	Priority Not Claimed	Certified Copy Attached	
				YES	NO
			<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
			<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
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			<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
			<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

☐ Additional foreign application numbers are listed on a supplemental priority sheet attached hereto:

I hereby claim the benefit under Title 35, United States Code § 119(e) of any United States provisional applications(s) listed below.

Application Number(s)	Filing Date (MM/DD/YYYY)	<input type="checkbox"/> Additional provisional application numbers are listed on a supplemental priority sheet attached hereto.
60/148,508	12 August 1999	

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Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

## DECLARATION

I hereby claim the benefit under Title 35, United States Code §120 of any United States application(s), or § 365(c) of any PCT international application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT international application in the manner provided by the first paragraph of Title 35, United States Code § 112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations § 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

U.S. Parent Application Number	PCT Parent Number	Parent Filing Date (MM/DD/YYYY)	Parent Patent Number (if applicable)

☐ Additional U.S. or PCT international application numbers are listed on a supplemental priority sheet attached hereto.

As a named inventor, I hereby appoint the following registered practitioner(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

Attorney Name	Reg. No.
Arvie J. Anderson	45,263
Lynn D. Apelgren	45,341
Robert A. Armitage	27,417
Brian P. Barrett	39,597
Michael T. Bates	34,121
Roger S. Benjamin	27,025
Gary M. Birch	48,881
William R. Boudreaux	35,796
Steven P. Caltrider	36,467
Paul R. Cantrell	36,470
Charles E. Cohen	34,585
Donald L. Corneglio	30,741
Gregory A. Cox	47,504
Paula K. Davis	47,517
Elizabeth A. Dawalt	44,646
John C. Demeter	30,167
Manisha A. Desai	43,585
Joanne Longo Feeney	35,134
Paul J. Gaylo	36,808
Francis O. Glnah	44,712
Janet A. Gongola	48,436
Amy E. Hamilton	33,894
Frederick D. Hunter	26,915
Thomas E. Jackson	33,064
Charles Joyner	30,466
Gerald P. Kelaheer	43,707

Attorney Name	Reg. No.
James J. Kelley	41,888
Paul J. Koivuniemi	31,533
Robert E. Lee	27,919
Kirby Lee	47,744
James P. Leeds	35,241
Nelsen L. Lentz	38,537
Douglas K. Norman	33,267
Aileen Palmberg	40,422
Thomas G. Plant	35,784
Edward Prein	37,212
Grant E. Reed	41,264
James J. Sales	33,773
Michael J. Sayles	32,295
Robert L. Sharp	45,609
David M. Stemerick	40,187
Mark J. Stewart	43,936
Robert D. Titus	40,206
Robert C. Tucker	45,155
Tina M. Tucker	47,145
MaChari Vomdran-Jones	36,711
Gilbert T. Voy	43,972
Thomas D. Webster	39,872
Lawrence T. Welch	29,487
Alexander Wilson	45,782
Dan L. Wood	48,613

☐ Additional registered practitioner(s) named on a supplemental sheet attached hereto.

Direct all correspondence to:

Name	ELI LILLY AND COMPANY.		
Address	ATTN: JOHN C. DEMETER		
Address	LILLY CORPORATE CENTER/DG-1104		
City	INDIANAPOLIS	State	INDIANA
Country		ZIP	46285
Telephone	(317) 276-3785	Fax	(317) 276-3861

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Name of Sole or First Inventor:

☐ A Petition has been filed for this unsigned inventor

Given Name	James	Middle Name	Web	Family Name	Kassebaum	Suffix e.g. Jr.	
Inventor's Signature	<i>James Web Kassebaum</i>			Date	1-25-02		
Residence: City	Indianapolis	State	IN	Country	USA	Citizenship	USA
Address	9221 Leeward Court						
Post Office Address	SAME AS ABOVE						
City	Indianapolis	State	IN	Zip	46256	Country	USA

☒ Additional Inventors are being named on supplement sheet(s) attached hereto.

Please type a plus sign (+) inside this box ☐

PTO/SB/01 (8-96) (MODIFIED)

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## DECLARATION

2-0

Name of Additional Joint Inventor, if any:				<input type="checkbox"/> A Petition has been filed for this unsigned inventor			
Given Name	Paul	Middle Name	Thomas	Family Name	Pugh	Suffix e.g. Jr.	
Inventor's Signature	<i>Paul Thomas Pugh</i>					Date	11/21/02
Residence: City	Knightstown	State	IN	Country	USA	Citizenship	USA
Address	8312 South Mill Road						
Post Office Address	SAME AS ABOVE						
City	Knightstown	State	IN	Zip	46148	Country	USA

3-0

Name of Additional Joint Inventor, if any:				<input type="checkbox"/> A Petition has been filed for this unsigned inventor			
Given Name	William	Middle Name	Webster	Family Name	Thompson	Suffix e.g. Jr.	
Inventor's Signature	<i>William Webster Thompson</i>					Date	11/18/2002
Residence: City	Indianapolis	State	IN	Country	USA	Citizenship	USA
Post Office Address	5521 Overbrook Circle						
Post Office Address	SAME AS ABOVE						
City	Indianapolis	State	IN	Zip	46226	Country	USA

Name of Additional Joint Inventor, if any:				<input type="checkbox"/> A Petition has been filed for this unsigned inventor			
Given Name		Middle Name		Family Name		Suffix e.g. Jr.	
Inventor's Signature						Date	
Residence: City		State		Country		Citizenship	
Post Office Address							
Post Office Address	SAME AS ABOVE						
City		State		Zip		Country	

Name of Additional Joint Inventor, if any:				<input type="checkbox"/> A Petition has been filed for this unsigned inventor			
Given Name		Middle Name		Family Name		Suffix e.g. Jr.	
Inventor's Signature						Date	
Residence: City		State		Country		Citizenship	
Post Office Address							
Post Office Address	SAME AS ABOVE						
City		State		Zip		Country	